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L3 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1

AN 2004362217 MEDLINE

DN PubMed ID: 15087430

TI Pregnancy-associated plasma protein-a production in rat granulosa cells:

stimulation by follicle-stimulating hormone and inhibition by the oocyte-derived bone morphogenetic protein-15.

AU Matsui Motozumi; Sonntag Barbara; Hwang Seong Soo; Byerly Tara; Hourvitz

Ariel; Adashi Eli Y; Shimasaki Shunichi; Erickson Gregory F CS Department of Reproductive Medicine, University of California San Diego,

La Jolla, California 92093-0674, USA.

NC U54 HD12303 (NICHD)

SO Endocrinology, (2004 Aug) 145 (8) 3686-95. Electronic Publication:

2004-04-15.

Journal code: 0375040. ISSN: 0013-7227.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200408

ED Entered STN: 20040722

Last Updated on STN: 20040818

Entered Medline: 20040817

AB Pregnancy-associated plasma protein-A (PAPP-A) is the major IGF binding

protein-4 (IGFBP-4) protease in follicular fluid, consistent
with its

proposed role in folliculogenesis. Despite growing interest,
almost

nothing is known about how PAPP-A expression is regulated in any tissue.

Here we show that FSH and oocytes regulate PAPP-A expression in granulosa

cells (GCs). By in situ hybridization, ovary PAPP-A mRNA was markedly

increased by pregnant mare serum gonadotropin treatment, and the message

was localized to the membrana GCs but not cumulus GCs (CGCs) of dominant

follicles. To explore the mechanism, we used primary cultures of rat GCs.

Control (untreated) cells produced little or no PAPP-A spontaneously.

Conversely, FSH markedly stimulated PAPP-A mRNA and protein in a dose- and

time-dependent fashion. Interestingly, PAPP-A expression in isolated CGCs

was also strongly induced by FSH, and the induction was inhibited by added

oocytes. To investigate the nature of the inhibition, we tested the

effect of oocyte-derived bone morphogenetic protein-15 (BMP-15). BMP-15

alone had no effect on basal levels of PAPP-A expression by cultures of

membrana GCs or CGCs. However, BMP-15 markedly inhibited the FSH stimulation of PAPP-A production in a dose-dependent manner. The cleavage

of IGFBP-4 by conditioned media from FSH-treated GCs was completely

inhibited by anti-PAPP-A antibody, indicating the IGFBP

-4 protease secreted by GCs is PAPP-A. These results

demonstrate stimulatory and inhibitory roles for FSH and BMP-15, respectively, in regulating PAPP-A production by GCs. We propose that FSH

and oocyte-derived BMP-15 form a controlling network that ensures the

spatiotemporal pattern of GC PAPP-A expression in the dominant follicle.

L3 ANSWER 2 OF 8 MEDLINE on STN

DUPLICATE 2

AN 2002654650 MEDLINE

DN PubMed ID: 12414897

TI Pregnancy-associated plasma protein A proteolytic activity is associated

with the human placental trophoblast cell membrane.

AU Sun Irene Y C; Overgaard Michael T; Oxvig Claus; Giudice Linda C CS Department of Gynecology and Obstetrics, Center for Research on

CS Department of Gynecology and Obstetrics, Center for Research on Women's

Health and Reproductive Medicine, Stanford University Medical Center,

Stanford, CA 94305-5317, USA.

NC HD 35789-05 (NICHD)

SO Journal of clinical endocrinology and metabolism, (2002 Nov) 87 (11)

5235-40.

Journal code: 0375362. ISSN: 0021-972X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200212

ED Entered STN: 20021105

Last Updated on STN: 20021217

Entered Medline: 20021209

AB Pregnancy-associated plasma protein-A (PAPP-A) is a product of the

placenta and decidua and is secreted into the maternal circulation during

human pregnancy. It recently has been identified as an IGF binding

protein (IGFBP)-4 protease. Presumed functions at the maternal-fetal

interface are to proteolyze IGFBP-4 and thus increase IGF bioavailability

locally in the placenta, to promote IGF-II-mediated trophoblast invasion

into the maternal decidua, and to modulate IGF regulation of steroidogenesis and glucose and amino acid transport in the villous.

Herein, we have investigated the possibility that IGFBP-4 proteolysis may

occur on the trophoblast cell membrane, presumably to increase local

bioavailable IGF for interactions with cognate IGF membrane receptors.

Human trophoblasts were cultured, trophoblast plasma membranes were

isolated and solubilized, and IGFBP-4 protease activity and PAPP-A

immunoreactivity in the solubilized plasma membrane fraction were investigated. IGFBP-4 protease activity was detected in solubilized human

trophoblast membranes, resulting in cleavage of recombinant human IGFBP-4

into 18- and 14-kDa fragments, detected by Western immunoblot analysis.

This protease activity was dependent on the presence of IGF-II, and its

metal ion dependence was demonstrated by inhibition of the protease by the

metal chelators, EDTA and EGTA. The presence of PAPP-A in solubilized

human trophoblast membranes was demonstrated by Western immunoblotting.

Trophoblast membrane PAPP-A had a relative molecular weight of approximately 200 kDa and comigrated on (reducing) SDS-PAGE with recombinant human PAPP-A and PAPP-A secreted into media conditioned by

cultured human trophoblasts. IGFBP-4 protease activity was not detected

after immunodepletion of PAPP-A from the trophoblast membrane fraction

with PAPP-A polyclonal antibodies, suggesting the identity of the membrane-derived IGFBP-4

protease as PAPP-A. Immunocytochemistry revealed PAPP-A on the cell membrane and in the cytoplasm of human trophoblasts in culture.

Together, these data demonstrate the presence of an IGF-II- and metal-dependent IGFBP-4 protease activity in human trophoblast plasma

membranes, identified as PAPP-A, which is well situated to proteolyze

IGFBP-4 at the maternal-placental interface to facilitate IGF action at

the villous surface and/or the invading extravillous cytotrophoblast.

L3 ANSWER 3 OF 8 MEDLINE on STN

DUPLICATE 3

AN 2002255160 MEDLINE

DN PubMed ID: 11994388

TI Identification and regulation of the IGFBP-4 protease and its physiological inhibitor in human trophoblasts and endometrial stroma:

evidence for paracrine regulation of IGF-II bioavailability in the

placental bed during human implantation.

AU Giudice L C; Conover C A; Bale L; Faessen G H; Ilg K; Sun I; Imani B; Suen

L-F; Irwin J C; Christiansen M; Overgaard M T; Oxvig C

CS Department of Gynecology and Obstetrics, Stanford University Medical

Center, Stanford, California 94305, USA.. giudice@stanford.edu

NC U54 HD31398 (NICHD)

SO Journal of clinical endocrinology and metabolism, (2002 May) 87 (5)

2359-66.

Journal code: 0375362. ISSN: 0021-972X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200206

ED Entered STN: 20020508

Last Updated on STN: 20020615

Entered Medline: 20020614

AB The IGF family plays an important role in implantation and placental

physiology. IGF-II is abundantly expressed by placental trophoblasts, and

IGF binding protein (IGFBP)-4, a potent inhibitor of IGF actions, is the

second most abundant IGFBP in the placental bed, expressed exclusively by

the maternal decidua. Proteolysis of IGFBP-4 results in decreased

affinity for IGF peptides, thereby enhancing IGF actions. In the current

study, we have identified the IGFBP-4 protease and its inhibitor in human

trophoblast and decidualized endometrial stromal cell cultures, and we

have investigated their regulation in an effort to understand control of

IGF-II bioavailability at the placental-decidual interface in human

implantation. IGFBP-4 protease activity was detected in conditioned media

(CM) from human trophoblasts and decidualized endometrial stromal cells

using (125) I-IGFBP-4 substrate. Identification of the IGFBP-4 protease as

pregnancy-associated plasma protein-A (PAPP-A) was confirmed by specific

immunoinhibition and immunodepletion of the IGFBP-4 protease activity with specific PAPP-A antibodies. The IGFBP-4 protease activity was IGF-II-dependent in trophoblast In

decidualized stromal CM, PAPP-A/IGFBP-4 protease activity was also

CM.

IGF-II-dependent, but was evident only when IGF-II was added in molar

excess of the predominant IGFBP in decidualized stromal cell CM, IGFBP-1,

supporting bioavailable IGF-II as a key cofactor of IGFBP-4 proteolysis by

PAPP-A. Cultured first and second trimester human trophoblasts (n = 5)

secreted PAPP-A into CM with mean +/- SEM levels of 172.4 +/-32.8

mIU/liter.10(5) cells, determined by specific ELISA. PAPP-A in trophoblast CM (n = 3) and did not change in the presence of IGF-II (1-100

ng/ml). Cultured human endometrial stromal cells (n = 4) secreted low

levels of PAPP-A (6.25 +/- 3.6 mIU/liter.10(5) cells). A physiological

inhibitor of PAPP-A, the proform of eosinophil major basic protein

(proMBP), was detected in trophoblast CM at levels of 1853 \pm +/-308

mIU/liter.10(5) cells, determined by specific ELISA, and was nearly

undetectable in CM of human endometrial stromal cells. Upon in vitro

decidualization of endometrial stromal cells with progesterone, PAPP-A

levels in CM increased nearly 9-fold without a concomitant change in

proMBP. In contrast to the experiments with trophoblasts, IGF-II and the

IGF analogues, Leu(27) IGF-II, and Des (1-6) IGF-II, resulted in a

dose-dependent decrease of PAPP-A levels in decidualized endometrial

stromal CM by 70-90%, and a dose-dependent increase in proMBP of 14- to

41-fold. The data demonstrate conclusively that the IGF-II-dependent

IGFBP-4 protease of human trophoblast and decidual origin is PAPP-A.

Furthermore, the differential regulation of decidual PAPP-A and proMBP by

insulin-like peptides supports a role for trophoblast-derived IGF-II as a

paracrine regulator of these maternal decidual products that have the

potential to regulate IGF-II bioavailability at the trophoblast-decidual

interface. Overall, the data underscore potential roles for a complex

family of enzyme (PAPP-A), substrate (IGFBP-4), inhibitor (proMBP), and

cofactor (IGF-II) in the placental bed during human implantation.

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DUPLICATE 4

AN 2001166450 EMBASE

TI Pregnancy-associated plasma protein-A is the insulin-like growth factor

binding protein-4 protease secreted by human ovarian granulosa cells and

is a marker of dominant follicle selection and the corpus luteum.

AU Conover C.A.; Faessen G.F.; Ilg K.E.; Chandrasekher Y.A.; Christiansen M.;

Overgaard M.T.; Oxvig C.; Giudice L.C.

CS Dr. L.C. Giudice, Dept GYN, Stanford University Medical Center, Stanford,

CA 94305, United States

SO Endocrinology, (2001) Vol. 142, No. 5, pp. 2155-2158. Refs: 24

ISSN: 0013-7227 CODEN: ENDOAO

CY United States

DT Journal; Article

FS 003 Endocrinology

010 Obstetrics and Gynecology

029 Clinical Biochemistry

LA English

SL English

ED Entered STN: 20010523

Last Updated on STN: 20010523

AB Insulin-like growth factors (IGFs), IGF binding proteins (IGFBPs), and

IGFBP proteases are important in ovarian function. IGFs stimulate

granulosa steroidogenesis, an effect that is inhibited by IGFBP-4 and

augmented by IGFBP-4 proteolysis. We have recently identified the IGFBP-4

protease in human ovarian follicular fluid (FF) as pregnancy-associated

plasma protein-A (PAPP-A). In the current study, we identify the IGFBP-4

protease secreted by cultured human ovarian granulosa cells as PAPP-A,

based on specific immunoinhibition and immunodepletion of the IGFBP-4 protease activity with PAPP-A

polyclonal antibodies and immunorecognition by PAPP-A
monoclonal antibodies in ELISA. PAPP-A was barely detectable in
conditioned media (CM) from granulosa derived from ≤ 9 mm
androgendominant follicles, but was secreted by cultured
granulosa from

estrogen-dominant follicles ≥ 9 mm, coincident with dominant follicle selection, and by luteinizing granulosa. PAPP-A levels in CM

from the latter did not change in response to IGF-II or hCG (100 $\mbox{ng/mL}$).

A naturally occurring inhibitor of PAPP-A, proform of eosinophil major

basic protein (proMBP), was detected by ELISA in estrogen-dominant

follicular fluid FF, but not in CM from granulosa or luteinizing granulosa

cells treated with IGF-II (0-200 ng/mL), FSH (0-100 ng/mL) or hCG (0-100

ng/mL), suggesting an alternative source (other than granulosa) for

proMBP, compared to PAPP-A. The data demonstrate granulosa cells as a

source of PAPP-A in human ovary and suggest that PAPP-A is a marker of

ovarian follicle selection and corpus luteum formation. In addition the

data suggest complex regulation of this system in human ovary.

L3 ANSWER 5 OF 8 MEDLINE on STN

AN 2001262826 MEDLINE

DN PubMed ID: 11316785

TI Pregnancy-associated plasma protein-a is the insulin-like growth factor

binding protein-4 protease secreted by human ovarian granulosa cells and

is a marker of dominant follicle selection and the corpus luteum.

AU Conover C A; Faessen G F; Ilg K E; Chandrasekher Y A; Christiansen M;

Overgaard M T; Oxvig C; Giudice L C

CS Endocrine Unit, Mayo Clinic, Rochester, Minnesota 55905, USA.

NC HD31579-07 (NICHD)

SO Endocrinology, (2001 May) 142 (5) 2155. Journal code: 0375040. ISSN: 0013-7227. CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals: Priority Journals

EM 200105

ED Entered STN: 20010521

Last Updated on STN: 20010521

Entered Medline: 20010517

AB Insulin-like growth factors (IGFs), IGF binding proteins (IGFBPs), and

IGFBP proteases are important in ovarian function. IGFs stimulate

granulosa steroidogenesis, an effect that is inhibited by IGFBP-4 and

augmented by IGFBP-4 proteolysis. We have recently identified the IGFBP-4

protease in human ovarian follicular fluid (FF) as pregnancy-associated

plasma protein-A (PAPP-A). In the current study, we identify the IGFBP-4

protease secreted by cultured human ovarian granulosa cells as PAPP-A,

based on specific immunoinhibition and immunodepletion of the IGFBP-4 protease activity with PAPP-A

polyclonal antibodies and immunorecognition by PAPP-A
monoclonal antibodies in ELISA. PAPP-A was barely detectable in
conditioned media (CM) from granulosa derived from </=9 mm
androgen-dominant follicles, but was secreted by cultured
granulosa from</pre>

estrogen-dominant follicles >/=9 mm, coincident with dominant follicle

selection, and by luteinizing granulosa. PAPP-A levels in CM from the $\,$

latter did not change in response to IGF-II or hCG (100 ng/mL). A

naturally occurring inhibitor of PAPP-A, proform of eosinophil major basic

protein (proMBP), was detected by ELISA in estrogen-dominant
follicular

fluid FF, but not in CM from granulosa or luteinizing granulosa cells

treated with IGF-II (0-200 ng/mL), FSH (0-100 ng/mL) or hCG (0-100 ng/mL),

suggesting an alternative source (other than granulosa) for proMBP,

compared to PAPP-A. The data demonstrate granulosa cells as a source of

PAPP-A in human ovary and suggest that PAPP-A is a marker of ovarian

follicle selection and corpus luteum formation. In addition the

suggest complex regulation of this system in human ovary.

DUPLICATE 5 L3ANSWER 6 OF 8 MEDLINE on STN AN 2001260195 MEDLINE PubMed ID: 11231911 DN TIInsulin-like growth factor binding protein-4 protease produced by smooth muscle cells increases in the coronary artery after angioplasty. AU Bayes-Genis A; Schwartz R S; Lewis D A; Overgaard M T; Christiansen M; Oxvig C; Ashai K; Holmes D R Jr; Conover C A Division of Cardiovascular Diseases, Mayo Clinic and Foundation, CS Rochester, Minnesota, USA. Arteriosclerosis, thrombosis, and vascular biology, (2001 Mar) SO 21 (3) 335-41. Journal code: 9505803. ISSN: 1524-4636. CY United States DTJournal; Article; (JOURNAL ARTICLE) LA English FS Priority Journals 200105 EΜ Entered STN: 20010521 ED Last Updated on STN: 20010521 Entered Medline: 20010517 AB Insulin-like growth factor (IGF)-I stimulates vascular smooth muscle cell (VSMC) migration and proliferation, which are fundamental to neointimal hyperplasia in postangioplasty restenosis. IGF-I action is modulated by several high-affinity IGF binding proteins (IGFBPs). IGFBP-4 is the predominant IGFBP produced by VSMCs and is a potent inhibitor of IGF-I action. However, specific IGFBP-4 proteases can cleave IGFBP-4 and liberate active IGF-I. In this study, we document IGFBP-4 protease produced by human and porcine coronary artery VSMCs in culture as pregnancy-associated plasma protein-A (PAPP-A). This was shown by a distinctive IGFBP-4 cleavage pattern, specific inhibition of **IGFBP** -4 protease activity with PAPP-A polyclonal antibodies, and immunorecognition of PAPP-A by monoclonal antibodies. Furthermore, we found a 2-fold increase in IGFBP-4 protease activity in injured porcine VSMC cultures in vitro (P<0.05). We also

evaluated IGFBP-4 protease/PAPP-A expression in vivo after

balloon injury. Twenty-five immature female pigs underwent

coronary artery

coronary

overstretch balloon injury, and vessels were examined at defined time

points after the procedure. Abundant PAPP-A expression was observed in

the cytoplasm of medial and neointimal cells 7, 14, and 28 days after

angioplasty (P<0.01 vs control). The highest PAPP-A labeling indices were

located in the neointima (36.1+/-2.1%) and the media (31.7+/-1.2%) 28 days

after injury. Western blot analysis confirmed increased PAPP-A in injured

vessels. PAPP-A, a regulator of IGF-I bioavailability through proteolysis

of IGFBP-4, is thus expressed by VSMCs in vitro and in restenotic lesions

in vivo. These results suggest a possible role for PAPP-A in neointimal

hyperplasia.

L3 ANSWER 7 OF 8 MEDLINE on STN

DUPLICATE 6

AN 2000066728 MEDLINE

DN PubMed ID: 10599745

TI Evidence that the insulin-like growth factor binding protein-4 protease in

human ovarian follicular fluid is pregnancy associated plasma protein-A.

AU Conover C A; Oxvig C; Overgaard M T; Christiansen M; Giudice L C CS Endocrine Research Unit, Mayo Clinic and Mayo Foundation, Rochester, MN

55905, USA.. Conover.Cheryl@Mayo.Edu

NC HD 31579-05 (NICHD)

SO Journal of clinical endocrinology and metabolism, (1999 Dec) 84 (12)

4742-5.

Journal code: 0375362. ISSN: 0021-972X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200001

ED Entered STN: 20000124

Last Updated on STN: 20000124

Entered Medline: 20000107

AB Ovarian insulin-like growth factor binding protein-4 (IGFBP-4) proteolysis

is involved in the regulation of follicular development, but until now the

identity of the responsible enzyme was unknown. In this study, we

identify the IGFBP4 protease in human follicular fluid as pregnancy

associated plasma protein-A (PAPP-A) based on distinctive IGFBP-4 cleavage

pattern, the same protease inhibitor profile, specific inhibition and

immunodepletion of IGFBP-4 protease activity

with PAPP-A polyclonal antibodies, and

immunorecognition by PAPP-A monoclonal antibodies in ELISA. Furthermore,

PAPP-A levels in estrogen-dominant and androgen-dominant follicular fluids

reflect their IGFBP-4 proteolytic activity. PAPP-A was also secreted by

human granulosa cells, the reputed source of IGFBP-4 protease activity in

follicular fluid. We have the molecular and biochemical tools to begin to

delineate the regulation and biological function of PAPP-A in normal and

dysregulated follicular development and atresia.

L3 ANSWER 8 OF 8 MEDLINE on STN

DUPLICATE 7

AN 1999179030 MEDLINE

DN PubMed ID: 10077652

TI The insulin-like growth factor (IGF)-dependent IGF binding protein-4

protease secreted by human fibroblasts is pregnancy-associated plasma

protein-A.

AU Lawrence J B; Oxvig C; Overgaard M T; Sottrup-Jensen L; Gleich G J; Hays L

G; Yates J R 3rd; Conover C A

CS Endocrine Research Unit, Mayo Clinic and Mayo Foundation, Rochester, MN

55905, USA.

NC AI09728 (NIAID)

DK07352 (NIDDK)

GM52095 (NIGMS)

SO Proceedings of the National Academy of Sciences of the United States of

America, (1999 Mar 16) 96 (6) 3149-53.

Journal code: 7505876. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199905

ED Entered STN: 19990601

Last Updated on STN: 20000303

Entered Medline: 19990520

AB Proteolytic cleavage of the six known insulin-like growth factor binding

proteins (IGFBPs) is a powerful means of rapid structure and function

modification of these important growth-regulatory proteins. Intact

IGFBP-4 is a potent inhibitor of IGF action in vitro, and cleavage of

IGFBP-4 has been shown to abolish its ability to inhibit IGF stimulatory

effects in a variety of systems, suggesting that IGFBP-4 proteolysis acts

as a positive regulator of IGF bioavailability. Here we report the

isolation of an IGF-dependent IGFBP-4-specific protease from human

fibroblast-conditioned media and its identification by mass spectrometry

microsequencing as pregnancy-associated plasma protein-A (PAPP-A), a

protein of unknown function found in high concentrations in the maternal

circulation during pregnancy. Antibodies raised against PAPP-A both inhibited and immunodepleted IGFBP-4

protease activity in human fibroblast-conditioned media.

Moreover, PAPP-A purified from pregnancy sera had IGF-dependent IGFBP-4

protease activity. PAPP-A mRNA was expressed by the human fibroblasts and

osteoblasts, and PAPP-A protein was secreted into the culture medium. In

conclusion, we have identified an IGF-dependent IGFBP protease and at the

same time assigned a function to PAPP-A. This represents an unanticipated

union of two areas of research that were not linked in any way before this

report.

Entrez PubMed Page 1 of 4







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Hourvitz A, Adashi EY, Shimasaki S,

Erickson GF.



Pregnancy-associated plasma protein-a production in rat granulosa cells: stimulation by follicle-stimulating hormone and inhibition by the oocyte-derived bone morphogenetic protein-15.

Endocrinology. 2004 Aug;145(8):3686-95. Epub 2004 Apr 15.

PMID: 15087430 [PubMed - indexed for MEDLINE]

Chen ST, Linkhart TA, Bagi G, Baylink DJ,
Qin X.



Studies on regulation of IGF (insulin-like growth factor)-binding protein (IGFBP) 4 proteolysis by pregnancy-associated plasma protein-A (PAPP-A) in cells treated with phorbol ester. Biochem J. 2004 Apr 1;379(Pt 1):57-64.

PMID: 14705967 [PubMed - indexed for MEDLINE]

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